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NEWS

Energy Deregulation: Licensing Tumors to Grow

Ken Garber*

Taking their cue from a controversial, 80-year-old theory of cancer, scientists are reexamining how tumors fuel their own growth and finding new ways to cut off their energy supply Sugar rush. PET scans reveal tumors (arrows) by highlighting areas of increased glucose uptake.

In a widely cited paper published 6 years ago, cancer biologists Robert Weinberg of the Massachusetts Institute of Technology and Douglas Hanahan of the University of California, San Francisco, described six hallmarks of cancer cells, including their ability to invade other tissues and their limitless potential to replicate. Last month, at the annual meeting of the American Association of Cancer Research, Eyal Gottlieb launched a lecture with this provocative claim: "I believe I'm working on the seventh element, which is bioenergetics."

Gottlieb, a biologist at the Beatson Institute for Cancer Research in Glasgow, U.K., notes that tumor cells need an unusual amount of energy to survive and grow. "The overall metabolic demand on these cells is significantly higher than [on] most other tissues," he says.

Tumors often cope by ramping up an alternative energy production strategy. For most of their energy needs, normal cells rely on a process called respiration, which consumes oxygen and glucose to make energy-storing molecules of adenosine triphosphate (ATP). But cancer cells typically depend more on glycolysis, the anaerobic breakdown of glucose into ATP. This increased glycolysis, even in the presence of available oxygen, is known as the Warburg effect, after German biochemist Otto Warburg, who first described the phenomenon 80 years ago. Warburg thought this "aerobic glycolysis" was a universal property of cancer, and even its main cause. Warburg won a Nobel Prize in 1931 for his earlier work on respiration, but his cancer theory was gradually discredited, beginning with the discovery of tumors that didn't display any shift to glycolysis. Ultimately, the ascendancy of molecular biology over the last quarter-century completely eclipsed the study of tumor bioenergetics, including Warburg's ideas. The modern view of cancer is that it's a disease of genes, not one of deranged energy processing.

Now, a revival in research on tumor bioenergetics suggests it could be both. A growing stream of papers is making the link between cancer genes and the Warburg effect, indicating that bioenergetics may lie at the heart of malignant transformation. For example, in a paper published online by Science this week (www.sciencemag.org/cgi/content/abstract/1126863), Paul Hwang's group at the National Heart, Lung, and Blood Institute in Bethesda, Maryland, reveals that p53, one of the mostly commonly mutated genes in cancer, can trigger the Warburg effect. And last year, Arvind Ramanathan and Stuart Schreiber of the Broad Institute in Cambridge, Massachusetts, reported that in cells genetically engineered to become cancerous, glycolytic conversion started early and expanded as the cells became more malignant. They concluded that the cancer-gene model and the Warburg hypothesis "are intimately linked and fully consonant." This idea remains controversial. Weinberg, for example, is a prominent skeptic. In his view, the Warburg effect and related metabolic changes are consequences of cancer, not major contributors to it: "It is a stretch to say that all this lies at the heart of cancer pathogenesis." Nevertheless, several companies and labs are now testing anticancer drugs designed to exploit the bioenergetics of tumors.

A new model of cancer

The revival in cancer bioenergetics began in the mid-1990s when radiologists showed that positron emission tomography (PET) imaging could detect and map many tumors. In PET, an injected glucose analog highlights tumors, which are hungrier for glucose than normal cells are. "PET imaging," says Schreiber, "suggests that the glycolytic switch even precedes the angiogenic switch": the point at which tumors begin making their own blood vessels.

Other evidence for metabolic differences in cancer accumulated at about the same time. Gregg Semenza of Johns Hopkins School of Medicine in Baltimore, Maryland, showed that a protein, hypoxia-inducible factor-1 (HIF-1), raised levels of glycolytic enzymes in cells lacking oxygen, and many hypoxic tumors contain elevated levels of HIF-1 (Science, 5 March 2004, p. 1454). In 1997, Chi Dang, also at Johns Hopkins, reported that the myc oncogene could turn on glycolysis. Furthermore, genes involved in energy production are mutated in several rare familial cancer syndromes.

One way that cancer cells might increase glycolysis is through Akt, an important pro-survival signaling protein. In 2004, Craig Thompson, a cancer biologist at the University of Pennsylvania, reported that activated Akt, independent of HIF-1, could convert cancer cells to start using glycolysis. Akt had earlier been shown to induce glucose transporters to take glucose into the cell, and Nissim Hay of the University of Illinois, Chicago, showed that Akt signals a glycolytic enzyme, hexokinase, to bind tightly to mitochondria, the organelles in which most of the cell's ATP is normally made during respiration. This allows hexokinase to use ATP from mitochondria to jump-start glycolysis. Thompson has since linked Akt to other glycolytic functions.

Thompson's model of how tumors make energy starts with upstream gene mutations that activate Akt and ends with cancer cells continuously consuming glucose, both aerobically and anaerobically. Others propose that cancer cells rely almost completely on glycolysis and largely shut down respiration, as Warburg originally reported. Because glycolysis is far less efficient than respiration, producing two ATPs per glucose molecule versus roughly 36 for respiration, that raises the question of how cancer cells benefit from the Warburg effect. "Is there a selective advantage?" asks Ajay Verma, a biologist at the Uniformed Services University of the Health Sciences in Bethesda, Maryland. "That hasn't been answered very well."

Cancer cells could benefit from glycolysis in many ways. Gottlieb and Thompson contend that a boost in glycolysis, added to respiration--which continues unabated--generates more energy more quickly than in normal cells that overwhelmingly rely on respiration. And because a glycolytic cancer cell is constantly slurping up nutrients, whereas a normal cell typically needs outside signals for permission to do this, such energy independence "empowers the [cancer] cell to grow," says Thompson. It doesn't need to break down amino acids and fatty acids to generate energy as most normal human cells commonly do and can turn them instead into the proteins and lipids necessary for growth.

Other potential benefits: Verma's work suggests that glycolysis leads directly to HIF-1 activation, which further boosts metabolism, and also stimulates angiogenesis and invasiveness. And in cases in which respiration is impaired, Dang suggests that shutting it down protects cancer cells from mitochondria damage that occurs when cellular respiration functions abnormally under hypoxic conditions.

But does the Warburg effect cause cancer, as Warburg claimed? Probably not. "The glycolytic shift is not absolutely required for transformation," says Thompson. But, he adds, it gives cancer cells "a higher metastatic potential and a higher invasive potential ... because they're now cell-autonomous for their own metabolism." Gottlieb agrees: "I believe [increased glycolysis] is important for sustaining tumors rather than inducing them."

Causality may not matter much when it comes to therapies. After all, angiogenesis doesn't cause cancer, but blocking it can stop cancer growth. Many early events in cancer "may not be relevant at the stages where we start treating those tumors," notes Gottlieb. "Well, the bioenergetic demand will always be there and will always be required."

Energy crisis

Drugs targeting tumor bioenergetics are on the way. Most exploit a tumor's increased reliance on glycolysis. Threshold Pharmaceuticals Inc., a biotech company in South San Francisco, California, is already testing two such drugs in cancer patients: a chemotherapy compound conjugated to glucose, and a glucose analog that cannot be metabolized, thus shutting down glycolysis.

Hexokinase, because it catalyzes the first step in glycolysis and can block cell death, is another key target. Hay, for example, proposes that drugs causing hexokinase to separate from mitochondria could treat cancer, by both damping down glycolysis, indirectly blocking a signaling

molecule called mTOR and causing apoptosis by another mechanism. Directly inhibiting the enzyme is another strategy. In 2004, Johns Hopkins researchers reported that a hexokinase inhibitor, 3-bromopyruvate, completely eradicated advanced glycolytic tumors in all mice treated. Chemists at the M. D. Anderson Cancer Center in Houston, Texas, are now developing 3-bromopyruvate analogs for eventual clinical trials.

Other potential drug targets exist. Last year, Thompson identified an enzyme, ATP citrate lyase, that allows cancer cells to overcome a natural check on glycolysis. Inhibiting it blocks growth of tumors in mice. And this March, Dang and Nicholas Denko of Stanford University in California separately reported that another enzyme, pyruvate dehydrogenase kinase (PDK), acts to shut down mitochondrial respiration and protect cells in low-oxygen conditions. "One can imagine that by blocking PDK activity we can actually trigger cells to commit suicide," Dang says.

Compounds that limit glycolysis would, in theory, kill cancer cells while sparing normal cells, which can burn amino acids and fatty acids for energy. "When [cancer] cells are engaged in high-throughput aerobic glycolysis, they become addicted to glucose," says Thompson. "So if you suddenly take away their ability to do high-throughput glucose capture and metabolism, the cell has no choice but to die."

How prevalent are glycolytic tumors? Using PET imagery, which maps glucose uptake, as a surrogate for the Warburg effect, Thompson estimates that between 60% and 90% of tumors make the shift to glycolysis. Gottlieb contends that most tumors turn to glycolysis only after oxygen disappears. But their special bioenergetics, he agrees, make them targetable by drugs. Some remain dubious. Michael Guppy, a biochemist recently retired from the University of Western Australia in Perth, even contends that the Warburg effect is a myth. Many researchers reporting the Warburg effect, Guppy says, do not accurately measure oxygen consumption in their cancer cells, sometimes ignoring the fact that cells can break down other molecules besides glucose to generate ATP. As a result, he contends, they overestimate the role of glycolysis. In a 2004 paper analyzing studies he found meeting his criteria for accuracy, Guppy reported that cancer cells, on average, were no more glycolytic than normal cells. So "a strategy for controlling cancer that relies on cancer cells being the sort of cell that cannot use oxygen when it's available ... is wrong," he says. Dang agrees that oxygen consumption could be measured more carefully but says Guppy "has ignored some key work in high-impact journals that negate his contention." He adds that the fact that PET detects tumors is more evidence for a high level of glucose uptake.

Even those at the vanguard of tumor bioenergetics acknowledge, however, that they must fully demonstrate how tumors inherently switch to glycolysis to meet energy needs. "We're still in the middle of absolutely proving that [system]," says Thompson. "It's a much more complex and dynamically regulated thing than anything else that we study in biology today." Until the results are in, the seventh hallmark of cancer may have to wait.

Ken Garber is a science writer in Ann Arbor, Michigan.

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